REMARKS

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Applicants wish to thank the Examiner for her helpful discussion of the application during the telephone conference of December 18, 2002. During the telephone conference the pending claims, outstanding enablement rejection, and the availability of the sequence of human osteonectin (SPARC) were discussed.

I. Amendment to the Specification

By this amendment, the specification has been amended to insert a sequence identifier in the last paragraph of page 11 of the specification and to append the sequence of human osteonectin in a sequence listing. The sequence is that provided in the Swaroop, *et al.* reference (*Genomics* 2:37-47, 1988) which was specifically incorporated in the specification by reference.

In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter. In accordance with 37 C.F.R. § 1.821(f), the paper copy of the Sequence Listing and the computer readable copy of the Sequence Listing submitted herewith in the above-identified application are the same.

II. Status of the Claims

By this amendment, claims 1, 10, 25, 26, 36, and 38 are sought to be cancelled, claims 6, 7, 8, 15, 16, 17, and 37 are sought to be amended, and new claims 39-55 are sought to be entered. Upon entry of this amendment, claims 6, 7, 8, 15, 16,

17, 37, and 39-55 are under consideration of which claims 39, 43, 44, 50, 52, and 55 are independent.

Support for the amendments to claims 6, 7, 8, 15, 16, and 17 can be found throughout the specification, *inter alia*, at page 5 fist and second full paragraphs.

Claim 37 has been amended to depend from newly presented claim 43.

Support for newly presented claims 39-42 may be found throughout the specification, *inter alia*, at page 5 last paragraph and in the Examples.

Support for newly presented claim 43 may be found throughout the specification, *inter alia*, at page 4, last paragraph to page 5, last full paragraph and in the Examples.

Support for newly presented claims 44-49 may be found throughout the specification, *inter alia*, at page 5, last paragraph and in the Examples.

Support for newly presented claims 50 and 51 may be found throughout the specification, *inter alia*, at page 6, third paragraph, page 7, last paragraph and Example 2.

Support for newly presented claims 52-54 may be found throughout the specification, *inter alia*, at page 8, first and second paragraphs and Example 2.

Support for newly presented claim 55 may be found throughout the specification, *inter alia*, at page 7, first paragraph.

No new matter has been introduced by these amendments.

III. The Rejection of Claims 6, 10, 15, 16, 17, 36 and 37 Under 35 U.S.C. § 112, First Paragraph Must Be Withdrawn

In the Office Action at pages 2 through 6, sections 2 and 3, claims 6, 10, 15, 16, 17, 36, and 37 have been rejected under 35 U.S.C. § 112, first paragraph, as the

specification allegedly does not enable one skilled in the art to make and use the claimed invention without undue experimentation. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 10 and 36 have been cancelled and claim 10 has been replaced by new claim 39 drawn to a method of treating a tumour in a human, comprising administering to cells of said tumour a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1 or a corresponding RNA sequence, wherein said nucleic acid molecule has the function of preventing or decreasing expression of human osteonectin. Claims 15, 16, 17 have been amended to depend from new claim 39. Claim 37 has been amended to depend from new claim 43 drawn to a composition comprising a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1 or a corresponding RNA sequence, wherein said nucleic acid has the function of preventing or decreasing expression in a cell of human osteonectin; and a pharmaceutically acceptable carrier. Insofar as the rejection of the cancelled claims may be applied to the new claims, Applicants offer the following remarks to overcome this rejection.

As stated in the MPEP:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

MPEP §2164.04.

The Examiner alleges that the specification would not enable one skilled in the art to make and used the presently claimed invention. In the Examiner's view, "[s]pecifically, under consideration of the guidelines presented in MPEP section 2164, it would have required undue experimentation to make and use the claimed methods of treatment at the time the invention was made." Office Action, page 3, second paragraph. Further, the Examiner asserts:

> Getting an antisense to work *in vivo* is a gene by gene and antisense by antisense process so that one antisense that functions *in vivo* does not correlate to an expectation of success for another antisense to the same gene or to antisense to other genes to function analogously *in vivo*. The diseases, routes of administration, vectors and antisense administered in the cited references thus do not correlate to the instantly claimed methods. The instant claims are broadly drawn to treatment of any type of tumor. The routes of administration would be expected to vary for treatment of any type of tumor in any whole organism. Further, the unpredictability of factors such as non-specific binding are sequence dependent factors which do not correlate among antisense to different genes of different sequences, sizes and modifications. Particular guidance is needed to teach a representative species of anti-osteonectin antisense to decrease tumors *in vivo* above what is taught in the specification as filed. Due to the unpredictability in the art, one of skill in the art would necessarily practice trial and error experimentation to make and use the claimed invention. Absent further guidance for the administration of the claimed antisense for the claimed treatments *in vivo*, one of skill in the art would necessarily practice undue experimentation to design a functional antisense for the claimed uses *in vivo*.

Office Action, pages 4 and 5.

Claim 39 as presently written requires treating a tumor by administering a nucleic acid molecule that binds to SEQ ID NO:1 (the human SPARC sequence from the Swaroop, *et al.* reference) and has the function of preventing or decreasing expression of human osteonectin. Given the sequence provided in SEQ ID NO:1, one

skilled in the art would have absolutely no difficulty in designing a nucleic acid molecule having these characteristics and using it to treat a tumor.

The references referred to by the Examiner provide ample evidence that successful antisense therapies were in existence at the time of the priority date. One skilled in the art, given the identification of osteonectin as a suitable target and armed with the knowledge of successful antisense therapies as shown in the cited references, would have had no difficulty in practicing the presently claimed invention.

As stated in the MPEP:

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).
>
> In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

MPEP § 2164.06

The Examiner asserts that getting antisense to work is a "gene by gene" process. While antisense therapy in general may be a gene by gene process, the present application specifically identifies the gene for osteonectin as an appropriate target. With regard to the Examiner's assertion that it is an "antisense by antisense process," the claim is restricted to nucleic acid molecules that result in preventing or decreasing osteonectin expression. The specification provides ample direction as to how to determine whether a nucleic acid molecule decreases or prevents osteonectin expression, for example, by Western blot using anti-SPARC antibodies. See Example 1 and Figure 1. The Examiner mis-characterizes this determination as "trial and error" experimentation. In fact, it is not undue experimentation at all. It is the kind of screening that is routinely practiced in the pharmaceutical industry. Given the teachings of the present specification, it would entirely routine for one skilled in the art to construct nucleic acid molecules that bind to SEQ ID NO:1 and to determine which of them has the ability to decrease or prevent osteonectin expression and use them to treat a tumor. While many nucleic acid molecules may be tested, such testing is routinely performed in the pharmaceutical industry.

Furthermore, the Examiner has failed to consider the impact of the "bystander effect" demonstrated in the present specification. At the time of the filing of the application to which the present application claims priority, many of the difficulties associated with treatments were caused by the need to transfect all or nearly all of the tumor cells in order to elicit a beneficial response, *i.e.*, shrinking or killing of the tumor. In the present specification, for example at page 32, second full paragraph and Table 3, it is demonstrated that the present invention provides a very potent response even when as few as 20% of the tumor cells are treated. The last column in Table 3 shows that when parental tumor cells are delivered at a ratio of 4:1 with cells treated

according to the invention, no tumors developed. Thus, using the teachings of the present invention, it is not necessary to transfect all the cells in a tumor in order to achieve a beneficial response thereby obviating many of the difficulties of the prior art.

Applicants respectfully submit that the specification would enable one skilled in the art to make and use the invention as presently claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

At pages 5 and 6 of the Office Action, the Examiner asserted that claim 6 was not enabled by the present specification. As previously written, claim 6 was drawn to the composition according to claim 1, wherein said antisense polynucleotide is an antisense RNA complimentary to human osteonectin mRNA. In the Examiner's view, "[t]he language "complementary to", broadly embraces antisense to human ostonectin which reads on sequences that are of any identity, and thus are not necessarily enabled as claimed per the limitations of claim 1." Office Action, page 5, second paragraph. Claim 1 has been cancelled and replaced by claim 43. Claim 6 has been amended to indicate that the antisense molecule binds to SEQ ID NO:1. Applicants respectfully submit that this rejection does not apply to the amended claim language and respectfully request its consideration and withdrawal.

IV. The Rejection of Claims 1, 6, 25, 26, and 38 Under 35 U.S.C. § 102(a), as Being Anticipated by Ledda, et al.

In the Office Action at pages 6-8, sections 4 and 5, claims 1, 6, 25, 26, and 38 were rejected under 35 U.S.C. § 102(aq) [sic, 102(a)] as allegedly being anticipated by Ledda, *et al.*, (*Medicina* (Argentina), 1996, 56(1):51-54, document AR6 of the IDS

filed October 28, 1999, hereinafter "Ledda"). Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 102(a) reads:

> A person shall be entitled to a patent unless
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign, before the invention thereof by the applicant for patent,

Applicants respectfully submit that the work described in Ledda is the Applicants' own work and that the co-author Laura Bover, not named as an inventor on the present application, did not make any inventive contribution to the presently claimed invention. Applicants submit herewith a Declaration signed by inventor Dr. Osvaldo Podhajcer, a co-author and named inventor, attesting to this fact. Accordingly, Ledda is not available as a reference against this application. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

V. The Rejection of Claims 1, 7, and 8 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Ledda, in view of Mercola, et al. Must Be Withdrawn

In the Office Action at pages 8-10, sections 6 and 7, claims 1, 7, and 8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ledda, in view of Mercola, *et al.* (*Cancer Gene Therapy*, 1995, 2:47-59, Ref AT7 of the IDS filed October 28, 1999, hereinafter "Mercola"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 1 has been cancelled and replaced with claim 43. Insofar as this rejection may be applied to new claim 43, Applicants have the following remarks. Claim 43 is drawn to a composition comprising a nucleic acid molecule comprising a sequence that binds to a polynucleotide comprising SEQ ID NO:1 or a corresponding

RNA sequence, wherein said nucleic acid has the function of preventing or decreasing expression in a cell of human osteonectin; and a pharmaceutically acceptable carrier. Claim 7 is drawn to the composition according to claim 43, wherein said nucleic acid molecule is conjugated to or administered in combination with a carrier molecule. Claim 8 is drawn to the composition according to claim 7, wherein said carrier molecule has a function selected from the group consisting of: increasing the solubility of the nucleic acid molecule, increasing the uptake into a cell of the nucleic acid molecule, slowing the breakdown of the nucleic acid molecule, preventing the breakdown of the nucleic acid molecule, and facilitating the manufacture of the nucleic acid molecule. Thus, all the claims require a nucleic acid molecule having a sequence that binds to a polynucleotide comprising SEQ ID NO:1. SEQ ID NO:1 provides the sequence of the cDNA encoding human osteonectin.

As stated in the MPEP:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143.

As discussed above, Ledda is not prior art to the presently claimed invention. In the absence of Ledda, the cited art neither discloses nor suggests a nucleic acid molecule that binds to SEQ ID NO:1; thus, the cited art does not teach the all the limitations of the present claims. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed

invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

Plasmids encoding antisense oligodeoxyribonucleotide to human osteonectin:
cDNAs encoding human SPARC (osteonectin), and their cloning, sequence and DNA manipulation have been described for example by:- Manson IJ, Taylor A, Williams JG, Sage H, and Hogan BLM, EMBO J 1986; 5: 1465-1472 'Evidence from molecular cloning that SPARC, a major product of mouse parietal endoderm, is related to an endothelial culture shock glycoprotein of Mr 43,000'- - giving sequence data, and incorporated herein by reference; and Swaroop A, Hogan BLM, and Francke U; Genomics 1988; 2: 37-47: 'Molecular Analysis of the cDNA for human SPARC/ osteonectin/ BM-40: sequence, expression and localisation of the gene to chromosome 5q31-q33', also giving sequence data and incorporated herein by reference (SEQ ID NO:1).

Claims 1, 10, 25, 26, 36, and 38 are sought to be cancelled without prejudice or disclaimer.

New claims 39-55 are sought to be entered.

6. (Four Times Amended) The composition according to Claim [1]43, wherein said [antisense polynucleotide]nucleic acid molecule is an antisense RNA that binds [complimentary]to human osteonectin mRNA.

7. (Thrice Amended) The composition according to Claim [1]43, wherein said [inhibitor]nucleic acid molecule is conjugated to or administered in combination with a carrier molecule.

8. (Twice Amended) The composition according to Claim 7, wherein said carrier molecule has a function selected from the group consisting of: increasing the solubility of the [inhibitor]nucleic acid molecule, increasing the uptake into a cell of the [inhibitor]nucleic acid molecule, slowing the breakdown of the [inhibitor]nucleic acid molecule, preventing the breakdown of the [inhibitor]nucleic acid molecule, and facilitating the manufacture of the [inhibitor]nucleic acid molecule.

15. (Thrice Amended) The method according to Claim [10]39, wherein said [antisense polynucleotide]nucleic acid molecule is an antisense RNA complimentary to human osteonectin mRNA.

16. (Thrice Amended) The method according to Claim 15, wherein said [inhibitor]nucleic acid molecule is conjugated to or administered in combination with a carrier molecule.

17. (Twice Amended) The method according to Claim 16, wherein said carrier molecule has a function selected from the group consisting of: increasing the solubility of the [inhibitor]nucleic acid molecule, increasing the uptake into a cell of the [inhibitor]nucleic acid molecule, slowing the breakdown of the [inhibitor]nucleic acid molecule, preventing the breakdown of the [inhibitor]nucleic acid molecule, and facilitating the manufacture of the [inhibitor]nucleic acid molecule.

37. (Amended) The composition of claim [1]43, wherein said composition is a pharmaceutical composition.